REMARKS

After entry of this amendment, claims 2-7, 10-16, 29, and 32-39 will be pending in the application. Claim 29 has been amended to more particularly point out and distinctly claim the invention. New claims 32-39 have been added. The amendments are fully supported by the specification as originally filed and no new matter has been added (*see, e.g.*, p. 6, *ll.* 23-30). Applicants respectfully request that the amendments and remarks made herein be entered into the record of the instant application.

1. THE PENDING CLAIMS SATISFY THE REQUIREMENTS OF 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 29, 2-5, and 10-16 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The rejected claims cover the administration of a drug to the intradermal compartment so that systemic distribution and the specified pharmacokinetic ("PK") profile is achieved.

Although the Examiner concedes that the specification is enabling for delivering insulin, PTH, and similar hormones, he contends that the disclosure is insufficient to support a method of delivering all drugs, at all pressures/flow rates, for any patient. *See*, Office Action at p. 3. Applicants respectfully disagree with this contention, and submit that the Examiner has erroneously focused on the working examples presented in the specification and not the teachings of the specification as a whole.

The Applicants take this opportunity to address how the guidance and working examples of the Pettis Application would enable the skilled artisan to deliver drugs intradermally and achieve the claimed pharmacokinetic profile. In support, the Applicants submit herewith the Declaration of Dr. Kasting ("Kasting Decl."). Dr. Kasting is a Professor

of Pharmaceutics and Cosmetic Sciences, with real-world experience in the field of transdermal drug delivery.

1.1 The Guidance and Working Examples of the Pettis Application Enable the Intradermal Administration of Drugs to Achieve the Claimed Pharmacokinetic Profile

As explained by Dr. Kasting, scientists in the art of drug delivery are concerned with obtaining systemic distribution of drugs in order to obtain the needed biological response for a particular therapeutic objective. Systemic distribution of a drug was (and still is) measured by monitoring the plasma drug concentration to determine the pharmacokinetics of the drug -- *i.e.*, the study of the time course of a drug and its metabolites in the body after administration by any route. For accurate measurement, blood is typically sampled frequently over time until the drug has cleared the system. There was a high level of skill in the art at the time of filing, and practitioners were prepared to conduct such pharmacokinetic studies in animal models to characterize the PK profile of a drug (Kasting Decl., ¶ 7). This is the audience by which enablement of the Pettis Application must be judged.

As shown by Dr. Kasting's analysis, the Pettis Application conveys ample guidance concerning the critical features of the invention, including working examples, that would enable such a scientist using ordinary skill to practice the invention. In particular, the Pettis Application describes the accurate positioning and placement of a needle of appropriate length, shape and structure to target the intradermal space (Kasting Decl., ¶ 10), as well as devices and mechanisms that could be used to apply appropriate pressure to control the rate of delivery through the needle (Kasting Decl., ¶ 11). The guidance does not stop there. The Pettis Application goes on to explain how the practitioner should start -- *e.g.*, by using visual inspection and other real time physical parameters to gauge the right amount of pressure to apply (Kasting Decl., ¶ 12). Given this guidance, as Dr. Kasting points out, the skilled artisan

would be prepared to carry out the routine experiments involved to determine the optimum pressures that can be used to achieve the claimed PK profile. (Kasting Decl., ¶¶ 12, 13 and 14). Once the optimum conditions are selected for delivering a given substance, then it can be applied reproducibly to practice the claimed method and obtain the desired PK profile as recited in claim 29 (Kasting Decl., ¶¶ 12 and 13). Based on the foregoing analysis, Dr. Kasting concludes that a skilled practitioner, using ordinary skill, would be able to successfully deliver drugs with the improved PK profile claimed. (Kasting Decl., ¶¶ 14, 15 and 16). Thus, the claims are enabled.

In the instant case, even by the Examiner's own admission, these routine experimental methods were *well known* to those skilled in the art (*see,* Office Action at p. 2). The mere fact that the blood sampling disclosed in the specification is over a period of 6 hours, and a number of experiments may be needed to arrive at the correct parameters to practice the claimed invention, does not make the experimentation "undue" by the *Wands* standard. *In re Wands*, 858 F.2d 731, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988). Here, as evidenced by Dr. Kasting's declaration, the experimentation required to determine the amount of pressure adequate to control the flow rate of any substance to the intradermal compartment may be done using methods well known in the art. A practitioner in the field of drug delivery would expect to periodically assay, over the course of 6 hours per injection, to determine optimal parameters for drug delivery. The Examiner proffers no basis for his contention that Applicant's data showing about 6 hours of experimentation per pressure value is considered undue in the field of drug delivery. The nature of drug delivery technology is such that it involves conducting a series of assays to determine the optimum conditions needed to provide a desired PK; these include generating a PK profile by measuring blood concentrations of a drug over a period of time, and graphing and analyzing PK profiles. These methods were well known and routinely used by those skilled in the art at the time of

the filing of the instant application. Practitioners of this art were prepared to do this work to arrive at the optimum conditions to be used for drug delivery. (*see*, Kasting Decl., ¶¶ 12 and 14).

Applicants submit that as emphasized in *Wands*, in the standard test for what constitutes "undue experimentation" the key word is "*undue*", not "experimentation". It appears, that the Examiner has based the enablement rejection on the necessity for *some* experimentation -- but, according to the legal standard, this is permissible. In fact a "*considerable* amount of experimentation is permissible, *if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.*" *In re Wands*, 858 F.2d at 737, citing *In re Jackson*, 217 U.S.P.Q. 804, 807 (Bd. App. 1982) (emphasis added). Experimentation by nature requires a certain amount of trial and error -- but experimentation alone is not considered "undue" so long as the methodology is *routine*. *In re Angstadt*, 190 U.S.P.Q. 214 (C.C.P.A. 1976).

1.2 The Premises For Non-Enablement Are Unfounded

The Examiner deems the specification enabling with respect to insulin, PTH and similar hormones, yet arbitrarily contends that the disclosure is not enabling with respect to other substances. The Examiner's arbitrary line drawing is unsupported. As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. §112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (C.C.P.A. 1970). Here, as evidenced by Dr. Kasting's Declaration the teachings of the specification, exemplified by the delivery of insulin and PTH, are sufficient guidance for one

skilled in the art to apply to other substances to achieve the claimed PK profile. (Kasting Decl., ¶¶ 8 and 9).

The Examiner also cites unpredictability of biological systems, particularly with respect to drug effects on individuals, as evidence that one skilled in the art would not be able to make and use the claimed methods of the invention. However, the particular physiological effect of a drug on the human body is not relevant to the enablement of the pending claims -- which are directed to the distribution of the drug in the body. The Examiner has conflated pharmacodynamics, *i.e.*, how the drug acts on the body, with pharmacokinetics, *i.e.*, how the body acts on the drug. The latter is the subject matter of the claimed invention. (*See*, Amendment filed July 10, 2003 for a detailed discussion). Thus, unpredictability associated with the effect of a drug's actions on a body, as cited by the Examiner, is not relevant to the PK profile of a drug. PK profiles are routinely used to evaluate optimum doses, formulations, and routes of administration. In fact, a given drug, when delivered in the same dose and route of administration, has a reproducible "fingerprint" PK profile; *see*, Kasting Decl., ¶ 12. Thus, the unpredictability of biological systems alleged by the Examiner as a factor, is not applicable to determining enablement of the claimed method.

The Examiner's point concerning Applicant's own "uncertainty" (Office Action, p. 3, 2d paragraph, referring to the use of the word "may" in the Pettis Application) is misguided and irrelevant to the enablement inquiry. The test for enablement is whether the ordinary skilled artisan (not the inventor) can use the guidance in the specification to practice the invention without undue experimentation -- the Applicant's alleged "uncertainty" does not factor into this equation. The evidence in this record shows the successful use of the claimed method for a good number of drugs (the Pettis Application itself; the first Pettis Declaration dated January 6, 2006), and that it could be practiced without undue experimentation (Kasting Decl., ¶¶ 13-16).

2. THE CLAIMS ARE NOT ANTICIPATED

Claims 29, 2, 3, 5-7, and 10-13 are rejected under 35 U.S.C. § 102(b) as anticipated by Gross *et al.* (U.S. Patent No. 5,848,991); Ganderton (U.S. Patent No. 3,814,097); or Autret (Autret et al., 1991, Therapie 46:5-8). The Examiner contends that Gross or Ganderton inherently anticipate the claims, and that Autret expressly anticipates the claims. For reasons detailed below, these rejections are erroneous and should be withdrawn.

2.1 The Claims Are Not Inherently Anticipated By Gross or Ganderton

The Examiner erroneously interprets Gross and Ganderton as disclosing the delivery of drugs to the intradermal compartment of a human subject's skin using a hollow needle having the features set forth in step (a) of claim 29, and incorrectly concludes that the resulting "plasma profile" (*sic*, pharmacokinetic profile) would be "inherently similar to, but higher as compared to subcutaneous injection." Taking the next leap of faith, the Examiner then asserts that one would somehow arrive at the right combination of needle length and pressure to inherently achieve the higher C_{max} and AUC recited in the claims (Office Action, p. 4). There is absolutely no proof in this record that practicing Gross or Ganderton would inherently achieve the PK profile required by the claims. In maintaining this inherency rejection, the Examiner notes that the Applicant has not shown any data to support the proposition that intradermal delivery would *not* inherently result in a higher C_{max} and AUC (Office Action, p. 6). The Applicants take this opportunity to supply the evidence requested by the Examiner and submit the Second Declaration of Dr. Pettis ("Second Pettis Decl.").

2.1.1 Mere Injection of A Drug To the IntraDermal Space Does Not Inevitably Result In The Pharmacokinetic Profile Claimed

Pharmacokinetics (PK) describes the concentration-time history of a drug in the body, and is typically represented graphically by plotting the concentration of the drug in the circulation over time. At least three parameters are typically used to characterize the PK for

delivery of a drug -- T_{max}, C_{max}, and AUC. T_{max} is the time required for the drug to reach a maximum serum concentration; C_{max} is the maximum (or peak) serum concentration of the drug reached within a given dose and route of administration; whereas the area under the serum concentration curve ("AUC") is a measure of bioavailability. (*See* Amendment dated July 10, 2003 at p.7). The claims require elevation of two of these three PK parameters as compared to subcutaneous delivery -- namely, C_{max} (a higher maximum plasma concentration), and AUC (a higher bioavailability); *e.g.,* claim 29.

The Second Pettis Declaration shows that mere injection of a drug to the intradermal compartment does *not inevitably* result in a higher C_{max} and AUC. Unless parameters are controlled -- as required by the claims -- delivery of substances to the intradermal space can result in an increased C_{max} and a decreased T_{max}, but nearly identical AUCs as compared to subcutaneous delivery (*see* Second Pettis Decl., ¶¶ 6-9); and in other cases, no difference between the C_{max} and AUC parameters is observed (Second Pettis Decl., ¶¶ 6, 7, 10 and 11).

While there is absolutely no evidence that practicing Gross or Ganderton would inherently result in the claimed PK profile, assuming *arguendo* these prior art methods were used to inject a drug into the intradermal space, the claimed PK profile would *not inevitably* result; *see*, *e.g.*, the Second Pettis Declaration.

In order for a prior art reference to inherently anticipate the claimed invention, the method disclosed must *inevitably* result in the claimed invention, *i.e.*, the claimed PK profile must be achieved *each time and every time* the methods of Gross and Ganderton are practiced. *In re Oelrich*, 666 F.2d 578, 212 U.S.P.Q. 323 (C.C.P.A. 1981); *Continental Can Co. USA Inc. v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 U.S.P.Q.2d 1746 (Fed. Cir. 1991); *Glaxo Inc. v. Novopharm Ltd.,* 52 F.3d 1043, 34 U.S.P.Q. 2d 1565 (Fed. Cir. 1995). In other words, each and every time Gross or Ganderton are practiced, the methods *must* deliver the drug into the intradermal compartment so that systemic distribution having the clamed PK

profile is obtained. As shown by Dr. Pettis, injection into the intradermal space, without more, does not inevitably result in a PK profile having a higher C_{max} and AUC as required by the claims. (Second Pettis Decl., ¶¶ 6-11). Since neither Gross nor Ganderton would *inevitably* lead to the PK profile claimed, inherent anticipation cannot be found.

There are many more reasons for why Gross or Ganderton could not anticipate the claims; some of these are elaborated below.

2.1.2 The Systems Of Gross And Ganderton Will Not Deliver Drugs Selectively Into The Intradermal Compartment

Dr. Kasting, a scientist eminently qualified in the field of drug delivery, has compared the systems of Gross and Ganderton to the invention. Based on his evaluation, he has concluded that the Gross and Ganderton systems will not deliver drugs selectively to the intradermal space.

GROSS

Contrary to the Examiner's assumption, the claimed features for the structure and placement of the needle (step (a) of claim 29) are not disclosed in Gross. As elucidated by Dr. Kasting, Gross' specification does not provide guidance to the skilled practitioner on how to target the intradermal compartment to achieve the claimed PK profile. Gross does not teach using a needle having an exposed height of 0 to 1 mm so that the needle penetrates the intradermal compartment and the needle's outlet depth and exposed height of the outlet are located within the intradermal compartment, as required by the claimed invention. (Kasting Decl., ¶¶ 21, 22, and 23). Gross also fails to appreciate the requirement for applying pressure in amounts sufficient to control the rate of delivery. (Kasting Decl., ¶ 24). The Examiner has thus improperly attributed teachings from the Applicant's own disclosure into the prior art.

As confirmed by Dr. Kasting, Gross does not describe, measure or evaluate the systemic distribution or pharmacokinetic profile of any drug (Kasting Decl., ¶ 25).

Therefore, Gross does not expressly anticipate the pending claims. Moreover, since as previously explained, practicing Gross does not inevitably lead to the PK profile required by the claims, inherent anticipation cannot be found.

GANDERTON

The dressing disclosed in Ganderton does not have the correct configuration to deliver a drug to the intradermal compartment of human skin for systemic distribution and attainment of a desired pharmacokinetic profile, which is required by the claimed invention. Instead, Ganderton discloses a permeable pad studded with spikes (solid or hollow) used for *topical application*. The pad is applied to the skin so that the spikes disrupt the top layer (the stratum corneum). Drug applied on top of the permeable pad (with or without the application of pressure) diffuses through the permeable pad onto the disrupted skin.

As elaborated by Dr. Kasting, the spikes in the Ganderton dressing (even if 1000μm in length as suggested by the Examiner) would not penetrate the intradermal space even if pressure is applied. (Kasting Decl., ¶ 20). Dr. Kasting's analogy of the Ganderton dressing to a "bed of nails" illustrates the point well. The application of pressure to the device results in distributing the force over the area encompassed by the "bed of nails," so that the force is dissipated, not concentrated. As a result, the force applied to any one spike is correspondingly reduced below the level required to pierce skin. Thus, even if Ganderton's spikes were hollow needles made at the maximum length specified by Ganderton (*i.e.* 1000 μm), the application of pressure would not result in delivering the drug through the lumen of the needles into the intradermal compartment so that the claimed pharmacokinetic profile is achieved. Instead, the drug would diffuse through the permeable pad (including the holes pierced through the pad) resulting in topical application and diffusion through the epidermis. Thus, Ganderton could not achieve the claimed pharmacokinetic profile and does not anticipate the claimed method.

In sum, the dressing in Ganderton does not have the proper structure to penetrate the intradermal space nor does it provide adequate pressure to control the rate of delivery of the drug and thus omits elements of the claimed invention. Moreover, as confirmed by Dr. Kasting, Ganderton does not describe, measure or evaluate the systemic distribution or PK profile of any drug, and therefore does not expressly anticipate the pending claims (Kasting Decl., ¶ 20). Since practicing Ganderton does not inevitably lead to the PK profile required by the claims, inherent anticipation cannot be found.

2.1.3 Request For Examiner's Affidavit

There is no evidence on this record that practicing the methods of Gross or Ganderton would inherently result in delivering a drug having the PK profile claimed. Moreover, the evidence of record shows that the claimed PK profile would not inevitably result from practicing the prior art. In the event the Examiner disagrees, and to the extent that any rejection is based on facts within his personal knowledge, applicants request that the Examiner provide an affidavit pursuant to the provisions of 37 CFR § 1.104(d)(2).

2.2 Autret Does Not Anticipate The Claims

The Examiner's contention that Autret achieves a higher AUC than subcutaneous delivery is incorrect -- Autret expressly states, and the data in Autret shows (Autret, Fig. 1), that the AUC obtained from Autret's mesotherapy approach is *no different from that obtained by subcutaneous injection.* (*See* Kasting Decl., ¶ 19). Thus, the rejection must fail.

The Lebel needle used in Autret does not have the structural features required by claim 29 (*see* Kasting Decl., ¶ 18). Moreover, the PK profile disclosed by Autret is *not* the one claimed by the Applicants. As explained by Dr. Kasting, the PK profile disclosed by Autret (*see* Autret, Fig. 1) is virtually identical to the profile for subcutaneous delivery, and

does *not* exhibit *both* a higher C_{max} *and* higher AUC, as is required by the pending claims. On this point, Dr. Kasting notes that Autret's characterization of its own data supports the Applicant's position. (Kasting Decl., ¶ 19). Autret expressly states at p. 5, Summary, "[*n*]*either* mean plasmatic levels at each plasmatic dosage *nor* mean *areas under the curve* ... [*i.e.*, the standard measure of bioavailability]... were significantly different" when Autret's method was compared to the subcutaneous route of administration. (Emphasis supplied). As summarized by Autret, "[i]n this study ... [Autret's method and subcutaneous routes of administration] ... are *not different* with regard to plasma levels ...". (Emphasis supplied).

Here, where the claims positively recite the requirement for an increased AUC, and the prior art reference clearly and expressly states that it lacks that claim element (and actually shows the data) it is difficult to imagine how a case for anticipation could possibly be alleged.

It appears that the Examiner has applied an incorrect approach for determining AUC. Briefly, bioavailability is used to describe the fraction of an administered dose of a drug that reaches the systemic circulation. In order to determine the bioavailability of a drug, a pharmacokinetic study is done to plot the *plasma concentration of drug over time*. For an accurate measurement, blood is sampled frequently over a long enough time to observe virtually complete drug elimination. (Kasting Decl., ¶ 7). The bioavailability is measured by calculating the "**a**rea **u**nder **c**urve" (AUC). In other words, the area of the PK profile spanning over the time points is calculated (represented in the figure below by the shaded region).

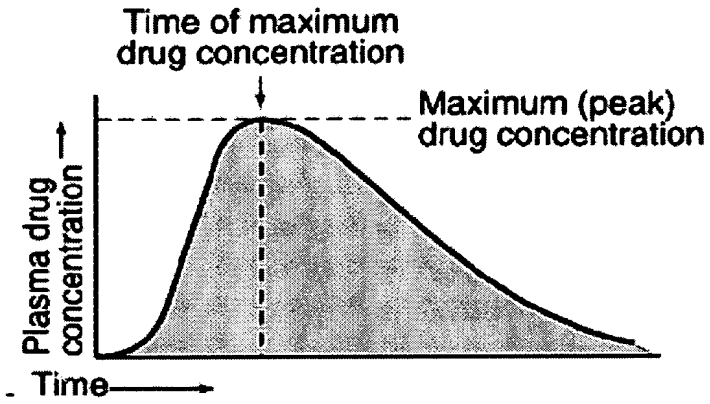

FIG. 298-1. Representative plasma concentration-time relationship after a single oral dose of a hypothetical drug. Area under the plasma concentration-time curve is indicated by shading. (Reproduced from Merck Manual of Diagnosis and Therapy, 1999, Clinical Pharmacology, reference CK of record).

In contrast to the art-accepted approach, the Examiner erroneously characterizes the AUC reported in Autret at a particular time point (1 hr) -- rather than the area under the curve (Office Action, p. 5, last paragraph). Clearly, AUC is *not* a measurement at one time point -- rather it is a measurement over a period of time. (*See* Kasting Decl., ¶ 7). Applying the proper mode of calculating AUCs to the PK profile of Autret, it is evident that the AUC of Autret's mesotherapy approach is *not* higher than the SC injection. This is confirmed by the authors of Autret and by Dr. Kasting (Kasting Decl., ¶ 19). The data do not support the Examiner's position, and the rejection based on Autret should be withdrawn.

3. THE CLAIMED INVENTION IS NOT OBVIOUS OVER GROSS IN VIEW OF PURI OR D'ANTONIO

Claims 29, 2, 3, 5-7, 10-13, and 16 are rejected under 35 U.S.C. §103(a) as obvious over Gross in view of Puri *et al.*, 2000, *Vaccine*, 18: 2600-12 ("Puri"), or U.S. Patent No. 6,056,716 to D'Antonio ("D'Antonio"). The Examiner contends that to the extent Gross does not inherently achieve the claimed pharmacokinetic profile -- this missing element is supplied

by Puri or D'Antonio. The obviousness rejection is based on the mistaken assertion that "Puri and D'Antonio disclose that intradermal injections give much greater C_{max} values than subcutaneous" (Office Action, p.5). The premise for this rejection is incorrect, and the rejection should be withdrawn.

Puri, which deals with vaccine delivery (not drugs) is concerned with the body's immune response to the vaccine -- in other words, how much antibody the body makes in response to vaccination -- not systemic distribution profiles, and certainly not C_{max} levels of the administered vaccine. To illustrate the point, at pp. 2609 - 2610 Puri describes an enhanced *immune response* -- as measured by a higher antibody response -- not an enhanced C_{max} and AUC of the vaccine substance as the Examiner contends!

D'Antonio relates to jet injection of vaccines and other substances -- not the intradermal delivery of drugs as claimed. Notably, at col. 29, line 3, cited by the Examiner, D'Antonio expressly states that the entire discussion (of the D'Antonio patent) focused on *intramuscular injection.* The remainder of that paragraph discusses the possibility of administering vaccines -- *not drugs* -- into the dermis, so that less antigen could be used to generate "an increasingly rapid and effective pick-up by the immune system" (D'Antonio, col. 29, ll. 23-26).

Unlike drugs, the efficacy and potency of vaccines are not evaluated using PK studies. By contrast, the efficacy of vaccines is typically evaluated by measuring their ability to confer a protective immunity in the host. Methods for assaying potency of immunogenic compositions such as vaccines include serologic testing such as measurement of antibody titers induced against the particular antigen. For example in Puri, an ELISA assay was developed to quantify antibody levels (not the injected vaccines) in the sera of immunized mice. Similarly, D'Antonio makes reference, not to a PK profile, but rather to a more rapid and effective pickup by the immune system.

The Examiner has improperly attributed parameters and properties of the drug delivery art to the vaccine art. Pharmacokinetic studies are meaningless in the vaccine art as practitioners in this field do not gauge the potency of the vaccine by its ability to be circulated systemically. In fact, as evidenced by the World Health Organization Guideline on Non-Clinical Evaluation of vaccine, pharmacokinetic studies, *e.g.*, determining serum or tissue concentrations of the vaccine are normally not needed and in fact shed no light on the efficacy of a vaccine.

Thus, neither Puri nor D'Antonio supply the pharmakinetic profile element missing from Gross; therefore, the combination does not render the claims obvious. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

4. MISCELLANEOUS

The Examiner's comments (Office Action, p. 6, first full paragraph) concerning the consistency of Applicant's arguments regarding the role of pressure in the claimed invention is not understood. Throughout this prosecution, the Applicants have maintained that the requirement of step (a) of claim 29 for inserting the needle, and the requirement of step (b) of claim 29 for pressure are critical for achieving the PK profile of the claims -- however, the absolute value of the applied pressure will vary depending upon the volume and nature of the formulation to be delivered. As explained in our previous response (January 6, 2005 at p. 7), in view of the guidance provided by the specification -- including the working examples -- the absolute value of the pressure used is not critical, in that it can be arrived at for a given formulation by a practitioner exercising ordinary skill. As verified by Dr. Kasting, the experimentation required is not "undue" (Kasting Decl., ¶¶ 13, 14, 15 and 16).

The Applicants hope that this discussion clarifies the matter raised by the Examiner.

5. CONCLUSION

The Applicant respectfully requests that the Examiner enter the amendments and consider the remarks made herein. Withdrawal of all rejections, and an allowance is earnestly sought. The Examiner is invited to call the undersigned attorney if a telephone call could help resolve any remaining items.

Respectfully submitted,

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